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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,403	HOLLADAY, LESLIE A.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/11/03, 9/1/04, and 1/31/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-27* is/are pending in the application.

4a) Of the above claim(s) *5-16 and 19-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,17,18 and 25* is/are rejected.

7)☒ Claim(s) *26 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

[2] Claims 1-2 and 4-27 are pending in the application.

[3] Applicant's amendment to the claims, filed 9/11/2003, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's arguments filed 9/11/2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[6] Claims 5-16 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/9/02.

[7] In the Office action mailed 12/24/2003, the examiner required further election of claims being examined on the merits. In view of applicant's arguments filed 3/29/2004, a supplemental restriction requirement was mailed 9/27/2004.

[8] Applicant's election with traverse of Group III, claims 2, 4, 17-18, and 25-27, in the response filed 1/31/2005 is acknowledged.

RESPONSE TO ARGUMENT: In the response filed 3/29/2004 (and reiterated in the response filed 1/31/2005), applicant argues there is no search burden on the examiner to co-examine the claims of Groups I-III as claim 1, which has already been examined, broadly encompasses the more limited claims, *e.g.,* claims 19, 22, and 25. Applicant argues that the scope of the search and examination of claim 1 would inherently cover any art that would apply to new claims 19-27. Applicant further argues that no search burden is required as the inventions have the same class and subclass.

Applicants' argument is not found persuasive. Regarding applicant's argument addressing the search burden, it is false to assume that the search of a broad "genus" claim will inherently cover a search for a limited "species" claim. For example, while a prior art reference or references may teach the invention of claim 1 reciting a genus of pharmaceutical polypeptide agents, the reference or references may not teach the invention of claim 1, wherein the pharmaceutical polypeptide agent is limited to a specific polypeptide, such as in claims 19, 22, and 25. "A genus does not always anticipate a claim to a species within the genus." See MPEP § 2131.02. As such, a separate search is required for each of the inventions of Groups I-III.

In response to applicant's argument that the inventions of Groups I-III have the same class/subclass, MPEP § 803 states that a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search. At least for the reasons stated above, the examiner has explained why a different field of search is required for each of the inventions of Groups I-III. As such, a serious burden on the examiner is required to co-examination the claims of Groups I-III, regardless of whether the inventions have or do not have the same classification.

Applicant argues the claim grouping is improper. Applicant's argument has been addressed and the alleged improper claim grouping remedied by the supplemental restriction requirement mailed 9/27/2004.

[9] The requirement is still deemed proper and is therefore made FINAL.

[10] Claims 5-16 and 19-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 3/29/2004 and 1/31/2005.

[11] Claims 1-2, 4, 17-18, and 25-27 are being examined on the merits.

Claim Objection

[12] Claim 18 is objected to as the claim does not end with a period.

[13] Claim 27 is objected to in the recitation of "histadine," which should be replaced with the proper spelling "histidine."

Claim Rejections - 35 USC § 112, Second Paragraph

[14] The rejection of claim 4 (¶ [8] of the Office action mailed 3/6/2003) is withdrawn in view of the amendment to the claim. It should be noted that, for purposes of examination, the term "biological activity" with respect to the polypeptide, has been interpreted as meaning "affinity of the [polypeptide] analog for its intended receptor" in accordance with the disclosure (p. 9, lines 6-9).

Claim Rejections - 35 USC § 112, First Paragraph

[15] The written description rejection of claims 1-2, 4, and 17-18 (¶ [9] of the Office action mailed 3/6/2003) is withdrawn upon further consideration. The examiner's reasoning for the rejection is more appropriate for the scope of enablement rejection under 35 U.S.C. 112, first paragraph, and not written description.

[16] Regarding written description of the "human growth releasing hormone" polypeptide as recited in newly added claims 25-27, the specification discloses that "[h]uman growth hormone releasing hormone (h-GHRH) is a 44 amino acid polypeptide containing glutamine residues at positions 16, 24, 30, 31 and 36 (SEQ ID NO:8)" (p. 13, lines 20-22). In this way, the specification specifically defines "human growth releasing hormone" polypeptide as being the polypeptide of SEQ ID NO:8.

[17] The scope of enablement rejection of claims 1-2, 4, 17-18, and 25 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [10] of the Office action mailed 3/6/2003) and the reasons stated below.

RESPONSE TO ARGUMENT: Applicant argues the specification teaches a skilled artisan how to make the full scope of recited synthetic analogs and how to use the analogs for electrotransport. Applicant argues that the similarity of His to Gln, Thr, and Asn results in the analog having a biological activity similar to that of the parent polypeptide because the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide are preserved in the analog.

Applicants' argument is not found persuasive. In this case, the claims are not limited to replacing Gln, Thr, and/or Asn with His. Instead, the claims broadly encompass an analog of any parent polypeptide, optionally human growth releasing hormone, having any amino acid or any combination of amino acids replaced with His. Further, there is no requirement that the resulting analog have the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide such that a skilled artisan would expect the analog to have such characteristics. The effect(s) of alteration of the amino acid sequence of a polypeptide, even a Gln to His alteration, is/are highly unpredictable (see "Introduction to Protein Structure," Branden and Tooze, Garland Publishing, Inc., New York, 1991, p. 247) as evidenced by Nishimura et al. and Steadman et al., the teachings of which are undisputed by applicant. The disclosure of the specification, including three working examples that teach substitution of Gln with His in three specific polypeptides, and the prior art references of Chien et al., Green et al., and Markussen et al., which teach practicing the claimed method using an insulin analog as the pharmaceutical polypeptide, fail to remedy the highly unpredictable nature of amino acid alteration on

the function of a polypeptide. As such, a skilled artisan must experiment, essentially by a trial and error process, to determine which analogs would retain the biological activity of the parent polypeptide such that the analogs would have the desired therapeutic effect. In view of the breadth of the claims, the lack of guidance and working examples, the high level of unpredictability and the amount of trial and error experimentation involved, undue experimentation is required for a skilled artisan to make and use the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

[18] The rejection of claims 1-2, 4, and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Chien et al. in view of Green et al. and Markussen et al. is maintained for the reasons of record (¶ [11] of the Office action mailed 3/6/2003) and the reasons stated below.

RESPONSE TO ARGUMENT: Applicant argues that the references are not properly combinable under 35 U.S.C. § 103(a); that the Chien et al. reference taken as a whole "teaches nothing even remotely related to the claimed process;" that the Chien et al. invention is a device where methods for enhancing delivery of pharmaceuticals are of no concern or interest; that the Green et al. teachings relate strictly to tripeptides and teaches away from its application to polypeptides because of an inverse relationship between electrotransport flux and molecular weight; that tripeptides and polypeptides are "so different that one of ordinary skill in the art . . . would not have been motivated by the simple tripeptide study . . . to practice the method of delivery of

the present invention"; that Green et al. do not suggest histidine substitutions in polypeptides; that polypeptides frequently consist of subunits as well as secondary, tertiary, and quaternary structures, which makes it "nearly impossible . . . to extrapolate from the results of studies of small molecules, such as tripeptides, to . . . polypeptides;" that Markussen et al. is unrelated to iontophoretic drug delivery or electrotransport; and that the references have no connection which provides a basis for their combination.

Applicant's argument is not found persuasive. The examiner maintains the position that the cited references are properly combinable and have connection which provides a basis for their combination. The three references teach all of the claimed limitations and are all intimately related to the subject matter of electrotransport of peptide compounds and insulin as an active preparation for administration. Since i) Chien et al. teach a device and methods for the electrotransport of insulin as a pharmaceutical agent, ii) Green et al. teach experiments to extend knowledge on enhancing electrotransport based on the protein structure to permeation relationship (see especially page 1122, left column, end of first full paragraph), and iii) Markussen et al. teach studies on insulin derivatives potentially useful in treating diabetes, the references are all related to a common field of endeavor concerning administration of peptide agents such as insulin to treat disease by means such as electrotransport.

As for applicant's assertions concerning Chien et al. and Markussen et al., the examiner notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck* 800 F.2d 1091, 231

USPQ 375 (Fed. Cir. 1986). Accordingly, the asserted deficiencies in Chien et al. concerning i) nothing related to the claimed process and ii) limitation to a device without relation to enhancing electrotransport are not persuasive because they are all fully addressed by the three cited references taken as a whole. Specifically, Green et al. provide the teachings and suggestions relating to the claimed process and electrotransport enhancement. More importantly, applicant's attempt to limit Chien et al. to the "device" taught therein is not appropriate because of the fact that Chien et al. teaches electrotransport methods comprising the use of the device (see column 11, line 56 through column 13, line 59). Similarly, the emphasis that Markussen et al. fails to teach or suggest electrotransport fails in light of Green et al.'s teachings. Thus applicant's assertions against Chien et al. and Markussen et al. individually are not persuasive.

As for Green et al. being limited to teaching tripeptides and teaching away from the invention which embraces electrotransport of polypeptides, the examiner notes that explicit within Green et al. is a discussion of evaluating electrotransport for transdermal delivery of peptide drugs and small proteins including insulin (see page 1122, left column, first full paragraph). Given such discussion and the explicit description of the experiments as meant to extend knowledge on enhancing electrotransport of drugs based on the protein structure to permeation relationship therein, applicant's assertion that an ordinary artisan would not find it obvious to apply Green et al. to larger peptides and polypeptides is unpersuasive.

Moreover, applicant's focus on the possible inverse relationship between electrotransport flux and molecular weight is misplaced because it is based on a tentative conclusion for anionic (negatively charged) compounds (see applicant cited portion of Green et al. on page 1126, paragraph bridging columns). The tentative nature of applicant's asserted inverse relationship is noted by Green et al. who state "one should recognize that further work with larger permeants is clearly needed in order to validate the true existence of this perceived trend" (see page 1126, top of right column). Moreover, the instant invention and the basis of the rejection are all concerned with the introduction of a histidine residue, as conducted by Green et al., to result in a cationic (positively charged) compound upon electrotransport. Accordingly, Green et al.'s tentative conclusion concerning an inverse relationship for anionic species cannot be readily applied to the instant case concerning a cationic species. While applicant appears to recognize this in their arguments, they proceed, without any additional support, to apply the conclusion anyway. This application is contrary to the teachings of Green et al., who specifically note that electrotransport of cationic species is distinct because the "fluxes do not attain steady state but increase progressively with time of iontophoresis" and that positively charged histidine "may bind to the fixed negative charges within the skin." Accordingly, the electrotransport of cationic species is significantly different from that of anionic species because the fluxes involved are different (steady state for anionic species and not steady state for cationic species such as histidine) and there may be an inherent bias favoring electrotransport of cationic compounds as taught by the reference.

As for the assertions concerning differences between tripeptides and polypeptides, the examiner notes that Green et al. specifically refer to experiments designed to examine the "building blocks" of protein molecules (page 1122, left column, end of first full paragraph). This clearly indicates that while the ordinary artisan knows of a difference, he would also find that information on the "building blocks" would be extendable to larger peptides and polypeptides. This was a basis for Green et al.'s experiments. Thus applicant's emphasis that Green et al. do not suggest histidine substitutions in polypeptides is unpersuasive because the lack of a direct suggestion is not fatal to a finding of obviousness where the suggestion would be obvious or implicit within a reference. Here, the suggestion that the experiments would be applicable to larger peptides and polypeptides is implicit within a particular passage from Green et al.

Finally, and regarding applicant's additional emphasis on the occurrence in polypeptides of subunits as well as secondary, tertiary, and quaternary structures, the examiner notes *a priori* that the issue of subunits is not applicable to the instant rejection based on insulin because it has no subunits. Moreover, all of these factors are well known to the ordinary artisan and as such are readily addressed by him in the form of knowledge concerning what amino acid residues may be involved in particular subunit interactions or higher order structure. The net analysis is that given the high degree of knowledge concerning the molecular structure of insulin, as indicated by Markussen et al., the ordinary artisan would readily focus on the introduction of histidine residues at positions that do not significantly impact a polypeptide's higher order structure, such as on the surface of the protein, unless that structure was dispensable.

Thus applicant's assertions concerning the complexity of polypeptides are unpersuasive.

Claim Rejections - Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[19] In the Office action mailed 9/27/2004, the examiner noted that a provisional double patenting rejection may be required and that the following Office action would be non-final. In the interest of compact prosecution, the examiner suggested that applicant submit a terminal disclaimer to avoid such a rejection. In the response filed 1/31/2005, applicant declined to submit a terminal disclaimer.

[20] Accordingly, claims 1-2, 4, 17-18, and 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 17-18 of US non-provisional patent application 08/466,610 (the '610 application). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by,

or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-2, 4, and 17-18 are generic to all that is recited in claims 1-4 and 17-18 of the '610 application. That is, claims 1-4 and 17-18 of the '610 application fall entirely within the scope of claims 1-2, 4, and 17-18 of the instant application. In other words, claims 1-2, 4, and 17-18 of the instant application are anticipated by claims 1-4 and 17-18 of the '610 application.

Also, claims 25-27 of the instant application and claim 1 of the '610 application are both drawn to methods of delivering a polypeptide through a body surface. The claims differ in the claims 25-27 limit the polypeptide used in the claimed method to human growth releasing hormone. The portion of the specification of the '610 application that supports a mutant human growth releasing hormone with Gln at positions 16, 24, 30, and 31 replaced with His as the polypeptide for delivery includes the embodiment disclosed at p. 10, line 14; p. 13, lines 20-29; and pp. 18-19 of the specification of the '610 application. Claims 25-27 cannot be considered patentably distinct over claim 1 of the '610 application when there is a specifically disclosed embodiment in the '610 application that supports claims 25-27 herein because it would have been obvious to one of ordinary skill in the art to use a mutant human growth releasing hormone with Gln at positions 16, 24, 30, and 31 replaced with His in the method of claim 1. One of ordinary skill in the art would have been motivated to do this

because that embodiment is disclosed as being a preferred embodiment within claim 1 of the '610 application.

Conclusion

[21] Status of the claims:

- Claims 1-2 and 4-27 are pending.
- Claims 5-16 and 19-24 are withdrawn from consideration.
- Claims 1-2, 4, 17-18, and 25 are rejected.
- Claim 26 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- Claim 27 is objected to for reasons stated above.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1656